UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/254,344	09/03/1999	YOSHIHIDE HAYASHIZAKI	024705-077	6838

7590 12/18/2001

BURNS DOANE SWECKER & MATHIS
PO BOX 1404
ALEXANDRIA, VA 223131404

EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	13

DATE MAILED: 12/18/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/254,344	Applicant(s) HAYASHIZAKI ET AL.	
	Examiner Richard G Hutson	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 September 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants previous amendment of claims 4, 6, 7, 8, 10, 15, 24 and 25 in Paper No: 6, 11/10/1999, is acknowledged. Claims 1-25 are at issue and are present for examination.

Applicant's election with traverse of Group I, Claims 1-23 and 25, drawn to an RNA polymerase mutant modified to enhance its ability to incorporate 3'-deoxyribonucleotides and a method for its production, is acknowledged.

Applicant's traversal is on the ground(s) that the searches required to completely examine the claims would substantially overlap and therefore would be coextensive. Applicants support this assertion by drawing attention to the fact that both groups set forth in the restriction requirement share a special technical feature which is pivotal to the invention, that is mutations which allow the incorporation of 3'-deoxyribonucleotides. It is noted that previously these groups were determined to not share a special technical feature based on Hayashizaki Yoshihide (JP 11075898 A) who teaches a variant RNA polymerase modified so as to improve the ability to incorporate 3'-dNTP. In response to this determination of lack of unity applicants have submitted translations of the priority documents: Japan Patent Application No. 155759/1998 and Japan Patent Application No. 180883/1997. It is noted that applicants have submitted copies of the translations of the above priority documents, not the "Japanese priority application (JP 11075898) " as recited in applicants responses of 7/27/2001 and 9/27/2001. While the submission of these documents would overcome a rejection or lack of unity based upon the earlier

used reference, Hayashizaki Yoshihide (JP 11075898 A), the lack of unity of invention between the two groups is maintained on the following basis.

Applicants assertion that both groups set forth in the restriction requirement share a special technical feature which is pivotal to the invention, that is mutations which allow the incorporation of 3'-deoxyribonucleotides, is not persuasive because applicant is reminded that claim 24 of group II is drawn to a polynucleotide encoding at least a part of a RNA polymerase of claim 1 and this reads on any polynucleotide which encodes a single amino acid of RNA polymerase (i.e. glutamine). Thus there is no shared special technical feature between groups I and II.

Further, Sousa et al. (EMBO Journal Vol 14, No. 18, pp 4609-4621, 1995) teach a mutant T7 RNA polymerase that efficiently utilizes deoxyribonucleotide triphosphates, thus in spite of applicants submission of a certified translation of the priority documents, there still exists no special technical feature shared between the groups.

The requirement is still deemed proper and is therefore made FINAL.

Claim 24 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper Nos. 11 and 12.

Priority

As mentioned above, applicants submission of translations of the priority documents: Japan Patent Application No. 155759/1998 and Japan Patent Application No. 180883/1997 is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892 or PTO-1449, they have not been considered.

Drawings

The drawings are objected to for the reasons stated on the Notice of Draftpersons Patent Drawing Review (PTO-948).

Correction is required.

Specification

The disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): 37 CFR 1.821. (d) states "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID

NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The sequence listing of the instant application lists 23 separate sequences, and while these sequences appear throughout the specification, there is no reference made to each of the sequences by sequence identifier as per 37 CFR 1.821. (d). Applicant is referred to Section 2422 of the M.P.E.P., Nucleotide and/or Amino Acid Sequence Disclosures in Patent Applications.

On page 4, line 3 of the specification the applicants list a reference, "Proc. Natl. Acid Sci. USA, 92:6339-6345, (1995)". It I suggested that the first named author of the reference also be included with the reference, and "Acid" should be "Acad".

On page 16, lines 18 and 26 of the specification in referring to the structural configuration of the RNA polymerase molecule, applicants state that specific loops "face the inside of the **crafts** in the polymerase molecule". This language is unclear and it is believed that applicants intended meaning is that the referred to loops "face the inside of the **cleft** in the polymerase molecule".

The description of Figure 16 is unclear because figure 16 comprises three sheets while the description only refers to "Figure 16". It is suggested that the figure and its description be amended to clearly communicate applicants intent, such as in figure 18 (1)-(4) and its corresponding description (i.e. Figure 16 (1)-(3)).

Appropriate correction is required.

Claim Objections

Claims 1, 3 and 7 are objected to because of the following informalities: Claim 1 recites "An RNA polymerase consisting of a wild type RNA polymerase at least one of amino acids in the wild type RNA polymerase is modified to enhance its ability for incorporating 3'-deoxyribonucleotides and derivatives thereof ...". This claim is grammatically awkward. A clearer recitation would read "An RNA polymerase consisting of a wild type RNA polymerase wherein at least one of the amino acids in the wild type RNA polymerase is modified to enhance [its] the ability of the RNA polymerase to [for] incorporat[ing]e 3'-deoxyribonucleotides and derivatives thereof into a polynucleotide..." In the interest of prosecution, the office interprets this claim as the suggested language.

Claim 7 recites "...ability for incorporating 3'-deoxyribonucleotides and derivatives thereof should be increased by twice..." A clearer recitation would read "the ability of the RNA polymerase to [for] incorporat[ing]e 3'-deoxyribonucleotides and derivatives thereof into a polynucleotide is [should be] increased [by] twice..."

Claims 3 and 10 recite "...deletion of amino acid..." A clearer recitation would read "...deletion of amino acid(s)..."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8, 10 and 25 are indefinite in that it is unclear what the metes and bounds are of those molecules considered to be encompassed by "3'-deoxyribonucleotides and derivatives thereof", specifically with respect to "derivatives thereof". The specification teaches that in this context derivative thereof means, for example, compounds composed of these 3'-deoxyribonucleotides which have a fluorescent label, but it is not clear if this is the metes and bounds of those molecules intended to be encompassed by a derivative thereof.

Claims 9, and 11-23 are indefinite in that they each recite specific amino acid residues of a RNA polymerase with out a reference sequence. It is suggested that a reference sequence be included when referring to specific amino acid residue. Reference to a "wild type RNA polymerase from T7 phage" is not sufficient to clearly designate a specific amino acid residue because within the art the numbering of amino acid residues of a common protein is not necessarily consistent.

Claims 2–5 are indefinite in the recitation of "a nucleotide binding site of a wild type RNA polymerase" because it is unclear what applicants consider to be included within the metes and bounds of such a site. While it is clear that the "nucleotide binding site" of the RNA polymerase is that site which binds the nucleotide substrate, it is unclear which amino acid residues constitute "a nucleotide binding site of a wild type RNA polymerase". That is which amino acid residues are considered within the metes

and bounds of the nucleotide binding site and which are not. The specification teaches that "the nucleotide binding site" of the polymerase can be for example, amino acids in a loop between the helix Y and the helix Z and/or amino acids in a loop between the helix Z and the helix AA of the wild type RNA polymerase (See top of page 16 and claim 6). Applicants further discuss the crystallography data of Sousa et al. (Nature, 364: 593-599, 1993) and refer to identified residues as constituting a part of the ribonucleotide binding site. Finally, applicants teach that the region corresponding to the amino acid residues 641-667 of the RNA polymerase derived from T7 phage correspond to the above-mentioned "nucleotide binding site". Based on above applicants disclosure as well as additional discussion by applicants that residues other than those corresponding to the loop and considered to face the inside of the "cleft" in the polymerase molecule, it is not clear which amino acids are considered to be within the metes and bounds of the "a nucleotide binding site of a wild type RNA polymerase". Additionally, while the specification discusses "the" nucleotide binding site of the RNA polymerase molecule, the rejected claims recite "a" nucleotide binding site of the RNA polymerase molecule, suggesting that their may be additional such sites and further adding to the lack of clarity of the recitation.

It is noted that claim 6 is drawn to the RNA polymerase of claim I, wherein the amino acid present in the nucleotide binding site is an amino acid in a loop between the helix Y and the helix Z and/or an amino acid in a loop between the helix Z and the helix AA of the wild type RNA polymerase. The office interprets the referred to region "a loop between the helix Y and the helix Z and/or an amino acid in a loop between the helix Z

and the helix AA of the wild type RNA polymerase" as being that as described in figure 5.

Claim 7 is drawn to the RNA polymerase of claim 1 which has been modified so that the ability for incorporating 3'-deoxyribonucleotides and derivatives thereof should be increased by twice in comparison with the wild type. This claim is indefinite in that it is confusing that the claimed RNA polymerase has been modified so that the ability for incorporating 3'-deoxyribonucleotides and derivatives thereof is "increased by twice" in comparison with the wild type. Since that data presented in Example 8 and Table I of the specification does not describe any mutant in which the ability for incorporating 3'-deoxyribonucleotides and derivatives thereof is "increased by twice" in comparison with the wild type, and the specification describes the RNA polymerase of the present invention as having the ability of incorporating 3-'deoxynucleotides and derivatives thereof **at least twice** higher than the wild type, in the interest of prosecution, the office has interpreted this claim as being drawn to the RNA polymerase of claim 1 which has been modified so that the ability for incorporating 3'-deoxyribonucleotides and derivatives thereof is increased by **at least** twice in comparison with the wild type. It is further noted that the office has interpreted the "increased ability for incorporating 3'-deoxyribonucleotides and derivatives thereof" as an increase in the amount of dNTPs relative to rNTPs incorporated into a reference polynucleotide in the presence of both dNTPs and rNTPs..

Claims 8, 9, 11 and 18- 23 each are drawn to a modified RNA polymerase "derived from" T7 phage, T3 phage, SP6 phage or K11 phage. It is unclear if "derived

from" includes more than just the introduction of the recited mutation into the natural wildtype polymerase. It is suggested that in each of these claims the recitation "derived from" be changed to "from" as this more clearly describes the origin of the modified RNA polymerase. In the interest of prosecution, this is how the office interprets these claims.

Claims 12, 15, 17, 19, 21 and 23 are indefinite in that they are unclear in the recitation "The RNA polymerase of the previous claim (i.e. 11, 14, 16, 18, 20 and 22)" with additional limitations outside the scope of the polymerases encompassed by the previous claim. Claim 11 for example recites "An RNA polymerase which is an RNA polymerase derived from T7 phage and has tyrosine at amino acid residue 644 or 667." Claim 12 is outside the scope of claim 11 as it encompasses "Am RNA polymerase which is an RNA polymerase derived from T7 phage and has tyrosine at amino acid residue 644 or 667", and thus claim 12 does not properly depend from claim 11, in that it does not further limit claim 11. Amendment of claim 12 such as "A RNA polymerase comprising a RNA polymerase of claim 11 with a further mutation..." Each of claims 15, 17, 19, 21 and 23 are similarly outside the scope of the claim from which they depend and should be amended in a manner similar to that discussed for claim 12 above.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12, 19, 21, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8, 10 and 25 are directed to all possible RNA polymerases consisting of a wild type RNA polymerase wherein at least one of the amino acids in the wild type RNA polymerase is modified to enhance its ability for incorporating 3'-deoxyribonucleotides and derivatives thereof in comparison with the corresponding wild type polymerase (claim 1), wherein at least one amino acid present in a nucleotide binding site of the wild type RNA polymerase has been modified (claim 2), wherein the modification of amino acid is substitution, insertion or deletion of an amino acid (claim 3), wherein the amino acid is replaced with a tyrosine or the replaced amino acid was a phenylalanine (claim 4 and 5), wherein the amino acid present in the nucleotide binding site is an amino acid in a loop between helix Y and helix Z and/or an amino acid in a loop between helix Z and helix AA (claim 6), wherein the RNA polymerase has been modified so that the ability for incorporating 3'-deoxyribonucleotides and derivatives thereof is increased by twice in comparison with the wild type (claim 7), and wherein said RNA Polymerase is derived from T7, T3, SP6 or K11 phage (claim 8), wherein said RNA polymerase has a further substitution, insertion or deletion of an amino acid other than the modification of claim 1 (claim 10), and a method of producing the RNA polymerase of claim 1 comprising preparing a nucleic acid molecule encoding an RNA polymerase, introducing a mutation into the nucleic acid so that one or more nucleotides in one or more regions would be changed and collecting a modified RNA polymerase expressed by the mutated nucleic acid molecule (claim 25). Claim 9 is directed to all

possible RNA polymerases wherein the wild type polymerase has been modified in a region corresponding to amino acid residues 641-667 of the wildtype RNA polymerase from T7 phage. Claims 12, 19, 21 and 23 are each directed to all possible mutant RNA polymerases of a wild type polymerase from T7, T3, SP6 or K11 phage comprising mutations in addition to those specific defined mutations. The specification, however, only provides the representative species of mutant RNA polymerases wherein the wildtype T7 phage RNA polymerase has a modification of amino acid residues 644, 665, or 667 of SEQ ID NO: 2 encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship beyond the disclosed species. The specification also fails to describe additional representative species of these mutant polymerases by any identifying structural characteristics or properties other than the activities recited in claim 1, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention which encompasses all mutants of all wildtype polymerases from all organisms with an enhanced ability for incorporating 3'-deoxyribonucleotides as well as additional mutants which retain this ability.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-10, 12, 19, 21, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for those mutant RNA polymerases wherein the wildtype T7 phage RNA polymerase has a modification of amino acid residues 644, 665, or 667 of SEQ ID NO: 2 and variants of SP6, K11 or T3 RNA polymerases with mutations in the amino acid residues corresponding to positions 644, 665 and 667 of T7 RNA polymerase, does not reasonably provide enablement for all mutations of all RNA polymerases from all organisms, which enhance the ability for incorporating 3'-deoxyribonucleotides and derivatives thereof, as well as additional mutants which retain this ability. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-10, 12, 19, 21, 23 and 25 are so broad as to encompass any RNA polymerases consisting of any wild type RNA polymerase wherein at least one of the amino acids in the wild type RNA polymerase is modified to enhance its ability for incorporating 3'-deoxyribonucleotides and derivatives thereof in comparison with the

corresponding wild type polymerase (claim 1), wherein at least one amino acid present in a nucleotide binding site of the wild type RNA polymerase has been modified (claim 2), wherein the modification of amino acid is substitution, insertion or deletion of an amino acid (claim 3), wherein the amino acid is replaced with a tyrosine or the replaced amino acid was a phenylalanine (claim 4 and 5), wherein the amino acid present in the nucleotide binding site is an amino acid in a loop between helix Y and helix Z and/or an amino acid in a loop between helix Z and helix AA (claim 6), wherein the RNA polymerase has been modified so that the ability for incorporating 3'-deoxyribonucleotides and derivatives thereof is increased by twice in comparison with the wildtype (claim 7), and wherein said RNA polymerase is derived from T7, T3, SP6 or K11 phage (claim 8), wherein said RNA polymerase has a further substitution, insertion or deletion of an amino acid other than the modification of claim 1 (claim 10), and a method of producing the RNA polymerase of claim 1 comprising preparing a nucleic acid molecule encoding an RNA polymerase, introducing a mutation into the nucleic acid so that one or more nucleotides in one or more regions would be changed and collecting a modified RNA polymerase expressed by the mutated nucleic acid molecule (claim 25). Claim 9 is so broad as to encompass any wild type RNA polymerase wherein the wild type polymerase has been modified in a region corresponding to amino acid residues 641-667 of the wildtype RNA polymerase from T7 phage. Claims 12, 19, 21 and 23 are so broad as to encompass any mutant RNA polymerases of a wild type polymerase from T7, T3, SP6 or K11 phage comprising mutations in addition to those specific defined mutations.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant RNA polymerase enzymes broadly encompassed by the claims, including all mutations of all RNA polymerases from all organisms, which enhance the ability for incorporating 3'-deoxyribonucleotides and derivatives thereof, as well as additional mutants which retain this ability. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the mutant RNA polymerases wherein the wildtype T7 phage RNA polymerase has a modification of amino acid residues 644, 665, or 667 of SEQ ID NO: 2.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any mutant RNA polymerase because the specification does not establish: (A) regions of the protein structure which may be modified without effecting RNA polymerase activity; (B) the general tolerance of RNA polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any RNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, extended experimentation would be required to determine which substitutions would be acceptable to retain the RNA polymerase activity claimed. As the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus having the claimed RNA polymerase activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any RNA polymerase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without

sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6-9 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Sousa et al. (EMBO Journal Vol 14, No. 18, pp 4609-4621, 1995).

Sousa et al. teach a T7 RNA polymerase (RNAP) that efficiently utilizes deoxyribonucleotide triphosphates. This mutant RNA polymerase, which comprises a substitution of Tyrosine 639 within the active site with phenylalanine (Y639F), has an enhanced ability for incorporating 3'-deoxyribonucleotides relative to 3'-ribonucleotides, in comparison with the corresponding wild type RNA polymerase. Sousa et al. teach that this mutant is approximately 20-fold less selective for rNTP over dNTP than the wild-type enzyme (See pages 4613, through 4614 and Table I.). Thus, the Y639 F mutant of Sousa et al. is 20-fold more selective for dNTP relative to rNTP. In addition to the T639F mutant, Sousa et al. also teach a number of additional mutants in the rNTP/dNTP selectivity assay including F644A, G 645A and Q649S (See page 4620,

right column under "Transcription reactions"). Sousa et al. also teach methods of producing the above RNA polymerases comprising introducing mutations into the nucleic acid molecule that encodes the RNA polymerase by site-directed mutagenesis and collecting the modified RNA polymerase expressed by the mutated nucleic acid.

Thus Sousa et al. anticipates a RNA polymerase consisting of a wild type RNA polymerase wherein at least one of the amino acids of the wild type RNA polymerase is modified to enhance its ability for incorporating 3'-deoxyribonucleotides and derivatives thereof in comparison with the corresponding wild type RNA polymerase (claim 1), wherein at least one amino acid present in a nucleotide binding site of the wild type RNA polymerase has been modified (claim 2), wherein the modification of amino acid is substitution, insertion or deletion of an amino acid (claim 3), wherein the amino acid present in the nucleotide binding site is an amino acid in a loop between helix Y and helix Z and/or an amino acid in a loop between helix Z and helix AA (claim 6), wherein the RNA polymerase has been modified so that the ability for incorporating 3'-deoxyribonucleotides and derivatives thereof relative to 3'-ribonucleotides should be increased by twice in comparison with the wildtype ((claim 7), and wherein said RNA polymerase is derived from T7, T3, SP6 or K11 phage (claim 8). Sousa et al. also anticipates a method of producing the RNA polymerase of claim 1 comprising preparing a nucleic acid molecule encoding an RNA polymerase, introducing a mutation into the nucleic acid so that one or more nucleotides in one or more regions would be changed and collecting a modified RNA polymerase expressed by the mutated nucleic acid molecule (claim 25).

Allowable Subject Matter

Claims drawn to a RNA polymerase comprising a wildtype T7 phage RNA polymerase which has a mutation of amino acid residues 644, 665, or 667 of SEQ ID NO: 2 would be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
December 13, 2001